REMARKS

The April 20, 2006 Official Action and the references cited therein have been carefully reviewed. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set forth in the April 20, 2006 Official Action. Therefore, the initial due date for response is July 20, 2006.

The Examiner states at page 2 of the Official Action that the trademark MATRIGEL has been used in the application and "should be capitalized where it appears and be accompanied by the generic terminology." Applicants have reviewed the application and found the trademark MATRIGEL to be used only once at page 8, line 10 wherein it is capitalized and described as "a basement membrane matrix containing, in addition to growth factors, collagen IV, laminin, entactin, and heparan sulfate proteogycan (perlecan)." Applicants submit that nothing more is needed.

The Examiner has rejected claim 18 on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over U.S. Patent 6,673,606.

Claims 15-18 and 22-24 have also been rejected for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

Lastly, the Examiner has rejected claims 19-21 under 35 U.S.C. §102(b) as allegedly being anticipated by Roecklein et al. (Blood (1995) 85:997-1005).

The foregoing rejections constitute all of the grounds set forth in the April 20, 2006 Official Action for refusing the present application.

In accordance with the instant invention, claims 19 and 22 have been amended, claims 25-36 have been added, and claims 20 and 21 have been cancelled. Support for the amendment to claim 19 can be found, for example, in claims 20

and 21. Support for the amendment to claim 22 can be found throughout the application including, for example, in original claims 1-3. Support for new claims 25 and 26 can be found, for example, at paragraphs [0065] to [0067]. Support for new claims 27-36 can be found, for example, at paragraph [0012].

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the present amendment and the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §112, first paragraph rejection of claims 15-18 and 22-24 and the 35 U.S.C. §102(b) rejection of claims 19-21, as set forth in the April 20, 2006 Official Action, cannot be maintained. These grounds of rejection are, therefore, respectfully traversed.

CLAIM 18, AS AMENDED, IS PATENTABLY DISTINCT OVER CLAIMS 1-4 OF THE '606 PATENT

The Examiner has rejected claim 18 on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over the '606 patent. It is the Examiner's position that claim 18 is anticipated by claims 1-4 of the '606 patent.

Applicants respectfully disagree with the Examiner's position. However, in the interest of expediting prosecution, Applicants have amended claim 18 to recite that the mesenchymal stromal cells are differentiated into neurons. Claims 1-4 of the '606 patent are drawn to methods of differentiating mesenchymal stromal cells into oligodendrocyte precursor cells. Accordingly, Applicants submit that claim 18, as amended, is clearly patentable over claims 1-4 of the '606 patent and, therefore, the instant rejection cannot be reasonably maintained. Withdrawal of the rejection of claim 18 on the grounds of nonstatutory obviousness-type double patenting is requested.

CLAIMS 15-18 AND 22-24, AS AMENDED, SATISFY THE ENABLEMENT REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected claims 15-18 and 22-24 for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. It is the Examiner's position that while the instant specification is enabling for generating oligodendrocyte precursor cells from mesenchymal stromal cells, the instant specification allegedly does not enable the skilled artisan to practice the full breadth of the instantly claimed invention. At pages 5-13 of the instant Official Action, the Examiner has considered the factors set forth in In re Wands, 8 USPQ2d 1400 (CCFA 1988), for determining whether the enablement requirement is satisfied. Applicants respectfully disagree with the Examiner's analysis.

It is a well settled premise in patent law that a patent need not teach, and preferably omits, what is well known in the art (see the MPEP at §2164.01).

The Examiner states at page 6 of the Official Action that the specification "lacks any description regarding the method (route, vectors types, dosage, patient profile) of preventing a human disorder disease associated with damaged myelin or neurological deterioration." Applicants strenuously disagree. At paragraphs [0065] to [0072], the instant specification describes methods of treating patients with CNS disorders. Notably, Neural Grafting in the Mammalian CNS (Bjorklund and Stenevi, eds., 1985) is incorporated by reference into the instant application as providing conventional techniques for grafting cells into the central nervous system. Further, the instant specification teaches that the cells may be administered by injection with a microsyringe into select regions of the brain (paragraph [0067]) including the cortex or basal ganglia (paragraph [0070]).

Applicants also note that claim 1 of U.S. Patent 5,082,670, issued on January 21, 1992, claims:

"A method for treating defective, diseased or damaged

cells in the mammalian central nervous system comprising grafting donor cell from the same mammalian species into the central nervous system, said donor cells genetically modified to produce a functional molecule in a sufficient amount to ameliorate said defective, diseased or damaged cells in the central nervous system."

35 U.S.C. §282 states that a "patent shall be presumed valid" and, as such, issued claims must satisfy all statutory requirements, including the enablement requirement of 35 U.S.C. §112, first paragraph. Notably, the '670 patent states that the defective, diseased, or damaged cells include those associated with "Alzheimer's or Parkinson's or injury from physical trauma" (column 8, lines 19-26). The '670 patent also cites Neural Grafting in the Mammalian CNS as providing methods for the transplanting of cells into the central nervous system. Accordingly, it is clear that methods for grafting cells into the central nervous system for treating defective, diseased or damaged cells located therein were fully enabled as of the priority date of the instant application.

In view of the foregoing, Applicants submit that it is evident, not withstanding the Examiner's comments to the contrary, that a skilled artisan was fully enabled to administer the cells of the instant invention to a patient.

At pages 7-9 of the Official Action, the Examiner cites certain references and concludes that as of the filing date in vivo cell therapy in humans was a highly unpredictable art. Applicants respectfully disagree. Indeed, as stated hereinabove, the USPTO clearly considered in vivo cell therapies in humans to be fully enabled by the issuance of the '670 patent in 1992 (see also recently issued U.S. Patent 7,022,231 which recites priority to April 1997 and claims methods of treating Parkinson's disease by administering cells transfected with a gene encoding a specific neurotropic factor). The skill of the artisan in the field was undoubtedly greater as of the priority date of the instant application than at the time of the '670 patent. Accordingly,

it is unclear how such methods could suddenly become non-enabled. Indeed, the MPEP states at §2164.03 that the "more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification."

Applicants also submit that the instant application has demonstrated that human mesenchymal stromal cells can be administered to mice via the lateral ventricle and that these stromal cells can differentiate into oligodendrocytes (see paragraphs [0077] to [0078]) and neurons (see paragraph [0079]). The Examiner, however, cites Orkin et al., published in 1995, as providing evidence of a "lack of a nexus between animal models to the human model." Okrin et al., as noted by the Examiner, reference a mouse cystic fibrosis model. Inasmuch as the instant invention is not concerned with cystic fibrosis, Applicants submit that the statement by Orkin et al. is irrelevant. Furthermore, Applicants note that Vogel et al., which is also cited by the Examiner in the instant Official Action, states in the context of cell therapy: "How easily can we translate what we know in the mouse to the human? There's nothing we've found that makes me think it can't be done" (page 1674). Accordingly, Applicants submit that, even based on the references cited by the Examiner, the skilled artisan would appreciate a nexus between animal models and the treatment of humans. Furthermore, the MPEP at §2164.02 states that "since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example." In view of the foregoing, Applicants submit that it is clear that the Examiner has failed to satisfy this burden for the instant enablement rejection.

The Examiner has also relied on the lack of specific therapy treatment protocols within the instant application. Applicants respectfully submit, however, that the MPEP at

§2164.01 states:

> "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." (Citations omitted.)

As set forth hereinabove, the prior art is replete with examples of the administration or grafting of cells into the central nervous system. Accordingly, Applicants respectfully submit that it cannot be considered undue experimentation for a skilled artisan to determine the specific dosing regimen for the instantly claimed methods.

Lastly, the Examiner cites Castro et al. (Science (2002) 297:1299) and states that "bone to brain trans-differentiation may not be a general phenomenon but may be dependent on the experimental system in which the hypothesis is tested and in this particular case, bone marrow cells failed to transdifferentiate into neural cells in vivo." Applicants respectfully disagree and submit herewith Mezey et al. (Science (2003) 299:1184b) which refutes the teachings of Castro et al. Indeed, Mezey et al. state that the experimental system used by Castro et al. was not an "ideal one" and that their "failure to detect LacZ-positive cells indicates that either their staining method failed or that the LacZ transgene was not expressed in their sample." Mezey et al. also provide numerous reasons as to why the LacZ marker was a poor choice and likely the root of the failure by Castro et al. to detect cells having undergone transdifferentiation. Lastly, Mezey et al. state that 1) they have "recently shown that bone marrow-derived cells enter the brain and differentiate into neural cells in humans," 2) that another report recently demonstrated that murine bone marrow cells were also capable of becoming neural cells, and 3) several groups have demonstrated that bone marrow cells give rise to microglia in the brains of transplanted animals. Accordingly, Applicants submit that the skilled artisan would readily

appreciate that the results obtained by Castro et al. are an artifact of the experimental system that they employed and, as such, the disclosure by Castro et al. would **not** make it "highly unpredictable that MSC would successfully differentiate into neurons and oligodendrocytes ... in vivo" as asserted by the Examiner.

In view of all of the foregoing, Applicants respectfully submit that the enablement rejection of claims 15-18 and 22-24 under 35 U.S.C. §112, first paragraph is untenable and request its withdrawal.

CLAIMS 19-21, AS AMENDED, ARE NOT ANTICIPATED BY ROECKLEIN ET AL.

The Examiner has rejected claims 19-21 under 35 U.S.C. §102(b) as allegedly being anticipated by Roecklein et al. Specifically, the Examiner contends that Roecklein et al. disclose immortalized mesenchymal stromal cells comprising an exogenous gene, namely the HPV E6/E7 genes.

In order to constitute evidence of lack of novelty under 35 U.S.C. §102(b), a prior art reference must identically disclose each and every element of the rejected claim. In re Bond, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990).

Applicants respectfully disagree with the Examiner's position. However, in the interest of expediting prosecution, Applicants have amended claim 19 to recite that the immortalized mesenchymal stromal cells comprise exogenously added hTERT. Roecklein et al. disclose generating immortalized human marrow stromal cells by transducing the cells with the human papilloma virus E6/E7 genes. Roecklein et al., however, fail to teach or suggest employing hTERT to immortalize the stromal cells. Indeed, Roecklein et al. state that bone marrow stromal cells cannot be immortalized by transformation with other genes such as c-myc, N-ras, and v-ras. Further, it is taught at pages 1001-1002 by Roecklein et al. that while bone marrow stromal cells can be generated with transformation with the SV40 large T antigen, these cell lines

may not be stable and exhibit differences in their "morphology and functional activity."

Inasmuch as Roecklein et al. fail to teach each and every element of the instantly claimed invention, Applicants submit that the instant rejection is untenable and should be withdrawn.

CONCLUSION

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the rejections set forth in the April 20, 2006 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to call the undersigned agent at the phone number given below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
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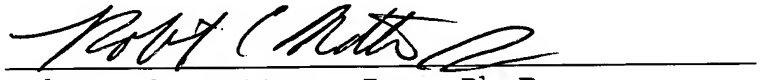
By 

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Enclosure: Mezey et al., Science (2003) 299:1184b